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REVIEW ARTICLE

Homologous Recombination and Its Role in Carcinogenesis

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Cancer develops when cells no longer follow their normal pattern of controlled growth. In the absence or disregard of such regulation, resulting from changes in their genetic makeup, these errant cells acquire a growth advantage, expanding into precancerous clones. Over the last decade, many studies have revealed the relevance of genomic mutation in this process, be it by misreplication, environmental damage, or a deficiency in repairing endogenous and exogenous damage. Here, we discuss homologous recombination as another mechanism that can result in a loss of heterozygosity or genetic rearrangements. Some of these genetic alterations may play a primary role in carcinogenesis, but they are more likely to be involved in secondary and subsequent steps of carcinogenesis by which recessive oncogenic mutations are revealed. Patients, whose cells display an increased frequency of recombination, also have an elevated frequency of cancer, further supporting the link between recombination and carcinogenesis.

INTRODUCTION

Genetic alteration is the fundamental underlying process that allows a normal cell to evolve into a cancerous one. Genetic alterations can take a variety of forms with the essential result being that a gene, or a combination of genes, is altered to produce a cell that can bypass normal growth restrictions. Here, we present a body of evidence indicating that one of the important processes of genetic alteration in the generation of cancers is homologous recombination (HR). Evidence from our laboratory, and many others, have demonstrated that certain genetic deficiencies result in higher than normal levels of genomic instability including a higher frequency of HR. Patients with such genomic instability have a higher probability of developing cancers as the instability allows a higher rate of genetic alteration. These alterations may result in either the direct mutation of an oncogenic gene or, more likely, it reveals an already mutated copy. In addition, we present evidence that proliferating cells demonstrate the highest propensity for HR, in effect this predisposes proliferating cancer cells to an increased frequency of this form of genomic instability.

MODELS OF CARCINOGENESIS

Here, we mention three commonly accepted models of carcinogenesis to highlight some of the processes that may involve an HR event. The simplest model for carcinogenesis is a one-step event. Most often, a mutation occurs in an oncogene that acts dominantly allowing oncogenesis. Examples of oncogenes include c-ABL1, H-RAS, c-MYC, c-ERBB, v-FOS, and *c-JUN* [1]. Alternatively, the one-step model involves an inherited recessive defect that is exposed by the mutation of its functional counterpart, though actually, this "mutation" is most often a loss of heterozygosity (LOH) event. These recessive mutations are usually in genes classically called tumour suppressers (for a review see [2]).

A simple two-step model allows for the majority of tumour suppresser genes being present as two functional copies, where both copies have to be mutated to incapacitate functionality [3]. In the published literature, LOH is the most commonly reported event, as opposed to mutational heterozygosity. Recombination, be it by deletion of the functional allele or gene conversion of the functional allele into the mutated one, is the most likely mechanism for LOH, this is discussed further later in this review.

A multistep scenario has intriguing implications. Here, the initial mutation is the result of a DNA repair or metabolism defect. Such cells may accumulate somatic mutations at a higher frequency or may have a higher level of gross genomic instability. Those patients with a predisposition to genomic instability have a much higher incidence of cancer than the general population, and they have a much earlier onset of certain tumor types. Some of these diseases are outlined later in the review.

As yet it has been difficult to determine which gene is initially mutated in most cancers. The reason is two-fold, firstly, the majority of tumours display heterogeneity [4, 5, 6, 7], often with an associated genetic instability [8, 9, 10, 11]. This phenotype may be facilitated by the initial mutation being of a DNA repair gene (see section *Genetic instability syndromes* below, for reviews see [6, 7]). Secondly, not all the genes

that are involved in carcinogenesis have been identified. However, it does appear that several cellular pathways are often altered to produce the necessary changes that produce a cancerous cell.

HOMOLOGOUS RECOMBINATION IN MAMMALIAN CELLS

Homologous recombination in mammalian cells is often considered to be less prevalent than an alternative recombination pathway, namely, nonhomologous end-joining (NHEJ) [12]. Thus, as a process of DNA repair and carcinogenesis, HR has often been overlooked [13]. This idea is widely accepted as it is well known that a large proportion of the mammalian genome contains repetitive DNA sequences [14]. *Contrarily*, recent studies have shown that mammalian cells are in fact quite proficient in HR; Liang et al [15] demonstrated that a site specific break between two copies of a gene will result in homologous deletion at a relatively high frequency (30% to 50%). Further, the author of [16] determined that sister chromatid exchange is highly prevalent [16], followed by homologous interchromosomal recombination and then by ectopic recombination [17, 18]. In the last decade we, amongst several other researchers, demonstrated that deletions can be mediated by HR between repeated DNA fragments [19] and that the frequency of these events are elevated following exposure to cancer-causing agents [20, 21, 22, 23].

HOMOLOGOUS RECOMBINATION IN CARCINOGENESIS

Homologous recombination may be playing a fundamental role in carcinogenesis. In the following sections we outline six situations where HR may have a fundamental part to play in the progression to cancer. Firstly, we believe that the HR can be a major mechanism in the LOH, fulfilling the second step of the two-step model or a later event in the multistep model. Secondly, there are some cancer prone diseases that have genetic instability as a phenotype, some of these diseases also display an elevated level of HR. An increased frequency of HR makes it more likely that the LOH will occur at an accelerated rate, but also raises the possibility that HR will cause aberrant genomic rearrangements that may act as the primary step towards carcinogenesis. We also present some recent evidence that HR is more prevalent in proliferating cells. Together, these arguments provide compelling evidence that HR may be an important factor in the multiple steps required for carcinogenesis.

Mechanisms of loss of heterozygosity

There are various mechanisms that can result in LOH. Basically, the LOH results from one allele being lost from a cell that is then either homozygous or hemizygous for the remaining allele. Homozygosity can be attained when a gene conversion event occurs. Hemizygosity occurs when one allele is lost, as its DNA is no longer present in the cell. This latter event may occur by the deletion of the region containing the gene or during the division by chromosome loss.

Gene conversion [14, 24, 25] is a unidirectional transfer of information. In such an event, DNA is copied [26, 27] from one chromosome or chromatid to another without necessarily altering the arrangement of flanking markers. The frequency by which this HR mechanism occurs is difficult to determine as most gene conversions probably go undetected. Much of our understanding of this and other recombination mechanisms comes from analogous comparison to work performed in the model organism *Saccharomyces cerevisiae*.

Chromosome loss is a major mechanism of LOH. This type of event results in a deviation in the chromosome number to produce a cell that is aneuploid. It is interesting to note that almost every type of histological cancer carries cells with highly heterogeneous patterns of aneuploidy (for review see [28]). Once aneuploid, cells are often genetically unstable, as seen in cases of congenital aneuploidy. Patients with this congenital abnormality often display a high incidence of neoplasia (for reviews see [29, 30]).

A translocation is the transfer of a part of one chromosome to a nonhomologous chromosome. Translocations are often reciprocal, exchanging two different DNA segments. The break point of a translocation event may occur within a gene, thus destroying its function or altering its expression pattern, for example, the Burkitt lymphoma. One such translocation, the Philadelphia chromosome (chromosome 9/22 translocation), which produces a *BCR-ABL1* compound gene and results in chronic myelogenous leukemia. Two studies mapped the breakpoint of the Philadelphia chromosome and found that the translocation was mediated by a region of shared homology [31, 32] implicating HR as the mechanism.

There are three basic mechanisms that may produce a DNA deletion event (see Figure 1), the replication slippage, intrachromosomal and interchromosomal recombination. The replication slippage during DNA synthesis may produce a deletion, these deletions tend to be small [33, 34, 35, 36, 37] and most often occurin special regions where short tandemly reiterated sequences exist. The most common example of this is microsatellite instability, a phenomenon most prominent in hereditary nonpolyposis colon cancer. The causative mutations of this disease are in the mismatch repair genes resulting in a lack of replication proofreading [38, 39, 40, 41] and, therefore, an increased frequency of replication errors.

Intrachromosomal deletions are the result of aberrant recombination, many times mediated by regions of homology and can remove very large regions of DNA. Such deletions have been identified as the cause of several diseases, which include X-linked ichthyosis where 1.9 Mb, megabases, of DNA are deleted mediated by flanking homologous S232 elements [42, 43], hereditary neuropathy with liability to pressure palsies where 1.5 Mb are deleted mediated by CMT1A-REP [44, 45, 46] as well as Prader-Willi syndrome [47], DiGeorge syndrome [48], and hypercholesterolemia [49], all these examples are due to deletions mediated by HR between flanking regions of homology. There are several mechanisms that may produce an HR mediated intrachromosomal deletion, three of the most likely being an intrachromosomal crossover

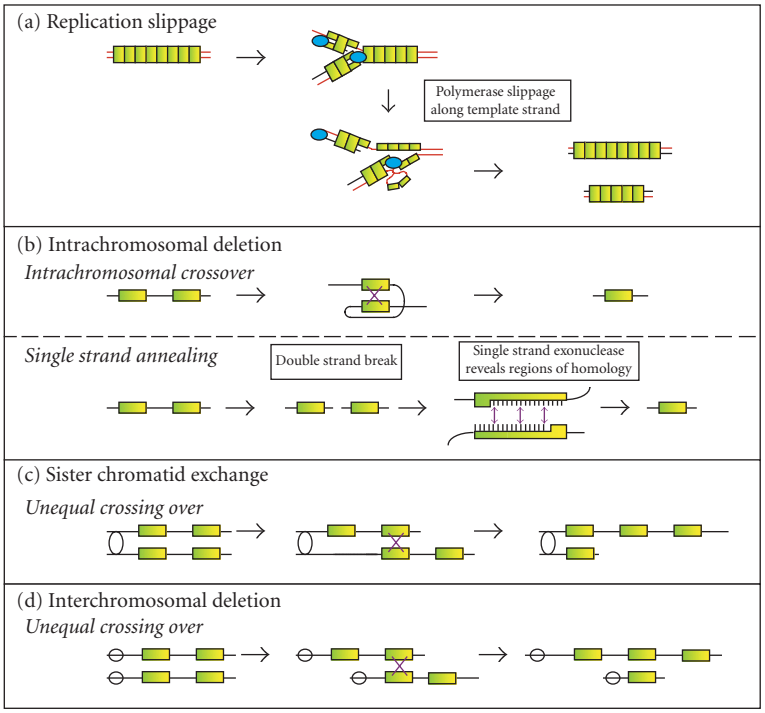

FIGURE 1. Mechanisms of deletion. (a) Replication slippage, where DNA polymerase dissociates from its template and reanneals to homologous sequences nearby resulting in either a deletion (shown) or insertion (not shown) of sequences. These tend to be relatively small deletions or insertions and are usually in regions of repetitive DNA. (b) Intrachromosomal or intrachromatid deletion may be mediated by a number of different mechanisms, two of the most likely being a crossover event and single strand annealing. A crossover event is mediated by aligning homologous sequences, strand invasion, possibly following a single-stranded break, allows strand exchange and recombination between the two homologous sequences. The result is a deletion of the intervening sequences. Single strand annealing is another likely mechanism that requires a double strand break between the homologous sequences. A single strand exonuclease can degrade one strand at the DNA ends until homology is revealed allowing the broken ends to anneal and the intervening sequences to be clipped off. (c) Interchormatid deletion is most likely to result from an unequal crossover event, only occuring in G2 after the chromatid has been replicated but before they are segregated. Again, the event is mediated by a repeated region of homology, but in these events two products are formed, a deletion and a triplication on the two resultant recombinant chromosomes. (d) Interchromosomal deletion is similar to interchromatid deletion except that the interaction is between homologous chromosomes.

event, single strand annealing (reviewed in [50]), or unequal sister chromatid exchange. Single strand annealing is initiated by a double strand break (DSB) in a nonhomologous region between repeats or within one repeat. DNA degradation of single strands from exposed 5′ ends of DSBs leads to single-stranded regions, which anneal with each other once the degradation has exposed the repeated sequences. The 3′ tails are processed and nicks are ligated, producing the deletion. Unequal sister chromatid exchange may occur during the DNA replication, probably initiated following the replication fork stalling [51]. A deletion results from an unequal crossing over between misaligned homologous regions on sister chromatids producing a deletion on one chromatid and a duplication of the same region on the other, these then segregate in the daughter cells that are produced. The final class of deletion is an interchromosomal event, this is very similar to an unequal sister chromatid exchange, except that the interaction is between homologous chromosomes or ectopic homologous regions and is not necessarily dependent upon replication. It should also be noted that the LOH by deletion can also be mediated by NHEJ. In these events, two ends of DNA are brought together by two or four bases of microhomology. Many of these types of event have been modelled in yeast [52] and human tissue culture cell systems [53].

Inter and intrachromatid recombination events are only distinguishable by the presence or absence of a reciprocal duplication product. In this respect, it is interesting to note that the Charcot-Marie-Tooth disease type 1A occurs from a duplication of the same region as is deleted in hereditary neuropathy with liability to pressure palsies [46, 54, 55]. Similarly, a tandem duplication within the *ALL-1* gene is mediated by *Alu* recombination and results in acute myeloid leukemia [56]. These duplications suggest that an interchromatid crossing over mechanism is responsible for these events.

Gene conversion, deletion, and perhaps translocation may be mediated by HR. In the past decade, we have used homologous deletion to detect genomic instability in a yeast model systems [57, 58], in human cells [22] as well as in vivo in mice [21, 23, 59]. Some of the most interesting results from these studies are presented later in this review.

Genetic instability syndromes

Assuming that genome rearrangements and deletion events cause a significant proportion of cancers, then there should be a correlation between those mutations that result in a higher recombination frequency and cancer predisposition. In fact, there are several genetic diseases that have a genetic instability phenotype and indeed have a high frequency of carcinogenesis. These include the Ataxia telangiectasia (AT) [60], Li-Fraumeni syndrome [61], Bloom syndrome [62], Werner syndrome [63], Cockayne syndrome, Fanconi anemia, Lynch syndromes I and II, Wiscott-Aldrich syndrome, and xeroderma pigmentosum [64]. Some of these diseases are presented in more detail below.

The Li-Fraumeni syndrome is a dominantly inherited disorder characterized by an early onset of cancer. The most prominent of these cancers are carcinoma of the breast followed by sarcomas, brain tumors, leukemia, lymphoma, lung carcinoma, and adrenocortical carcinoma, usually in children and young adults. The overall risk of cancer in these patients is nearly 100%, with over 50% of patients developing breast cancer by age 50 (reviewed in [65]). Li-Fraumeni syndrome patients, who carry a recessive mutation in *TP53*, have an exceptionally high risk of developing multiple primary cancers [66]. p53 has been proposed to be involved in maintaining the stability of the genome [61, 67, 68, 69, 70, 71, 72, 73, 74] by either its function in cell cycle arrest or apoptosis. At early passages, fibroblasts from *Trp53-/-* mice develop several chromosomal abnormalities [75]. Tumours from *Trp53-/-* mice are often aneuploid and there has been some evidence of chromosomal instability [76, 77]. In addition, p53 may inhibit HR via a putative interaction with the HR machinery protein RAD51 [71, 78]. How p53 is involved with HR is still not clearly understood, though many studies have undertaken to examine the relationship, most showing that cells lacking p53 have a higher than normal frequency of HR [71, 72, 73, 79, 80, 81].

Ataxia telangiectasia is an autosomal recessive syndrome. Among the phenotypes that patients display are chromosomal instability, radiosensitivity, and a predisposition to lymphoid cancer in childhood. Although AT is a relatively rare disorder, it has been estimated that about 1% of the general population is heterozygous for *ATM* mutations [82]. These heterozygous carriers may have a predisposition to sporadic breast cancer, though this correlation is still under discussion (for a review see [83]).

Cells from AT patients display chromosomal instability both spontaneously and following induction by ionizing radiation or radiomimetic agents (reviewed in [84, 85]). Cytogenetic analysis revealed a higher spontaneous incidence of chromosome breaks, chromosome gaps, acentric fragments, dicentric chromosomes, and aneuploidy. In addition, the T lymphocytes have an elevated frequency of translocations with break points mapping to the T-cell antigen receptor genes and the Ig heavy chain genes (reviewed in [85]). Following exposure to ionizing radiation or radiomimetic agents, cells from AT patients have an increased frequency of chromosomal aberrations compared to normal cells [60, 84, 85, 86]. In vivo, we have reported that Atm-deficient mice have an increased frequency of spontaneous HR [87]. In comparison, Turker et al demonstrated that, in the same mouse background, a deficiency in Atm did not result in an increased frequency of mutations [88], thus indicating that HR plays a more important role in the etiology of the AT.

ATM is generally thought to be important in activating p53 in response to the DNA damage [89, 90]. Recent reports have highlighted the multifunctional aspect of ATM, including that it phosphorylates BRCA1 [91, 92] and NBS [93, 94, 95, 96] following irradiation. In addition, there have been several reports linking ATM, through c-ABL1, to the HR protein RAD51 [97, 98, 99, 100]. Again, as with p53, how do these interactions relate to the HR is not fully understood, but it is an area of intense research.

A mutation in the *BRCA1* gene is estimated to confer a 70% risk of breast cancer by age 70 (reviewed in [101]). There have been numerous studies examining the frequency of breast cancers. From these studies, it is evident that mutations in the *BRCA1* and *BRCA2* genes result in an early onset of cancer and are responsible for a high percentage of premenopausal breast cancers (12% to 28%). The percentage depends on the prevalence of founder mutations within the population examined [102, 103, 104, 105, 106, 107, 108, 109, 110], the incidence of nonfamilial breast cancers tend to occur at a later age. Inactivation of *BRCA1* or *BRCA2* confers genetic instability such as aneuploidy and chromosomal rearrangements [111, 112, 113, 114, 115, 116]. In addition, both BRCA1 and BRCA2 play a role in HR, in the absence of either protein, HR repair of double-stranded breaks is defective [117]. It has been reported that BRCA1, BRCA2, and RAD51 form foci in the nucleus following the DNA damage [118, 119, 120] in an ATM-dependent manner [92].

RAD51, RAD52, and RAD54 are components of the RAD52 epistasis group [12, 121, 122], homologues of the genes defined in yeast to be necessary for an HR reaction. In vitro, it has been shown that RAD52 binds single-stranded tails at the sites of resected DSBs [123] as well as capping the exposed terminal nucleotide [124]. Both RAD51 and RAD54 form foci following the DNA damage [125]. In addition, the loss of RAD54 leads to recombinational deficiencies and DSB repair defects [126, 127]. The absence of RAD51 results in an accumulation of chromosomal abnormalities and cell death [128]. Both RAD51 and RAD54 have been shown to mediate sister chromatid exchange [129] and both form foci following exposure to ionising radiation, the kinetics of these foci are altered in ATM-deficient cells [130, 131]. How do the observed foci relate to the HR, is still unclear, but it does appear that BRCA1 is a component of several DNA damage response mechanisms [132] and may be responsible for activating HR in certain circumstances.

The genes mutated in Bloom's and Werner's syndromes, *BLM* and *WRN*, respectively, are highly homologous to RecQ helicase [133, 134], and were postulated to be involved in recombination. Cells from Bloom's syndrome patients show a high frequency of sister chromatid exchanges, hyper recombination, and chromosomal breakage. Patients with Bloom's

syndrome also show a greatly elevated predisposition to cancer of the sites and types that affect the general population [135]. Similarly, cells from Werner's syndrome patients show a 50-fold elevation in mutation rate, with the predominant form of mutations being gross DNA deletions [63]. The Werner syndrome patients age prematurely and show features like early onset of cataracts, generalized hair loss, loss of skin elasticity, osteoporosis, atherosclerosis, and short stature [136], they also often develop nonepithelial tumours and, to a lesser extent, leukemia, and carcinomata. These cancer prone diseases have in common a defect in genomic stability. Notably, both BLM and WRN have now been associated with processing the structures associated with stalled replication forks [137, 138], which may explain the observed phenotypes.

Fanconi's anemia (FA) is an autosomal recessive genetic disorder characterised clinically by progressive bone marrow failure, skeletal deformities, and a predisposition to neoplasia [139, 140]. Patient cells manifest an extreme chromosomal instability and hypersensitivity to polyfunctional alkylating agents. Most interstingly, cells from FA patients as well as cell extracts show a much elevated frequency of HR measured with plasmid constructs [141].

Although the AT has been identified to be the result of a mutation in the *ATM* gene, two other mutations result in syndromes that were originally mistaken to be AT. These variants of AT are caused by mutations in NBS (the syndrome is presently called Nijmegen breakage syndrome) [142] and in MRE11A [143], and present similar phenotypes, including genetic instability. NBS, MRE11, and RAD50 form a complex that NBS modulates once it is phosphorylated by the ATM in response to the DNA damage [93, 94, 95]. In yeast, it has been shown that RAD50 and MRE11 are involved in NHEJ [144, 145, 146], a mechanism that can repair double strand breaks and competes with HR. Assuming that the mammalian homologues of these genes are also involved in NHEJ, it seems plausible that a deficiency in ATM also results in a slight deficiency in NHEJ. Therefore, the damage would be channelled into HR as an alternative pathway, possibly explaining the hyper recombination phenotype that we found in Atm-deficient mice [87]. Most recently, it has been demonstrated that the WRN interacts with the Ku heterodimer [147], the complex thought to bind double strand break ends at the initiation of NHEJ [12, 148, 149, 150]. Thus, in a fashion similar to AT, a WRN deficiency may lead to an increased frequency of HR by default.

Susceptibility of proliferating cells to homologous recombination

Actively dividing cells are thought to be the most prone to developing cancer. Mitogenesis has been proposed to be an important contributor to carcinogenesis [151, 152] as evidenced by a higher risk for cancer after tissue regeneration. Furthermore, chemical carcinogenesis and transformation are most efficient if the target cells are treated just prior to or during the S phase [153, 154].

Using yeast to investigate the effect of the cell cycle arrest on the induction of deletions mediated by HR by different carcinogens, it was found that only DNA double strand breaks induce homologous deletion recombination in arrested cells, other forms of DNA damage such as DNA single strand breaks, UV lesions, as well as exposure to alkylating agents need DNA replication to induce homologous deletion recombination [155, 156].

As mentioned earlier, HR events are mediated by the RAD52 epistasis group. It is interesting to note that the protein and mRNA levels of this group tend to correlate with cell proliferation. For example, it has been reported that RAD51 expression is the highest in intestinal and uterine epithelia [157], which are highly proliferative. RAD51 has also proven to be essential in early mouse development [158, 159], a time of massive cellular proliferation. Consistent with the correlation with cell proliferation, both RAD51 and RAD54 are maximally transcribed in the S phase, during DNA synthesis [157, 160, 161, 162]. These observations are suggestive of a function for HR in proliferating cells, especially in combination with the damage inducibility of HR in proliferating cells. Takata et al [163], using chicken DT40 cells, demonstrated the involvement of NHEJ in G1 to early S phase, with HR functioning more in late S phase to G2. The role of replication was further demonstrated by Saintigny et al [164], who demonstrated that HR is increased in late S phase, only after the RAD51 foci formation. These studies strongly support the recent proposal that HR performs a special function during replication, namely, in resolving stalled replication forks [165, 166, 167, 168]. Altogether, it appears that HR is a common feature of the normal cell and may be especially harnessed by highly proliferative cancer cells.

CONCLUSIONS

In conclusion, we have presented a body of evidence that HR can play a role in different stages of carcinogenesis. While HR may contribute to the initial steps of carcinogenesis, we believe that HR functions mostly as a secondary or subsequent step in tumor progression. If genomic rearrangements and deletion events were the cause of a portion of the cancers, it might also be expected that certain carcinogens would increase the frequency of genome rearrangements. This has in fact been elegantly demonstrated in yeast [58, 169, 170], in human cells [22], as well as in vivo in mice [21, 23, 59]. With a wide variety of carcinogenic agents able to induce HR, it is easy to suggest that the normal day-to-day exposure to a variety of environmental and endogenous damages will also increase the frequency of HR. As can be observed in those patients who have an up regulated level of HR, an increased frequency of HR events can be highly deleterious. In addition, the sensitivity of proliferating cells to HR is highly correlative with proliferating cells being more prone to cancer and fits with current models of replication/recombination. Finally, the HR is likely to play a major role in producing the observed heterogeneity in many tumours. All in all, HR may be much more prevalent during carcinogenesis than previously considered.

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